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Synthesis of deuterium labeled compounds by KCN-assisted hydrolysis of phosphonium salts

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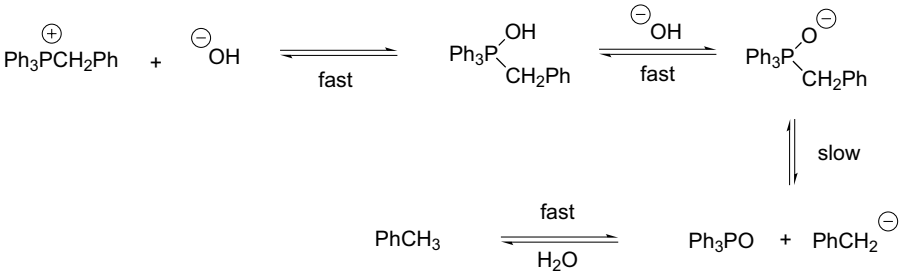
Abstract—We developed a facile deuterium labeling method for benzylic or allylic halides or acetates systems. Conversion of the halides or acetates to the corresponding phosphonium salts and the following mild hydrolysis with KCN afforded the deuterium labeled compounds in good yields.

Deuterium labeling experiments and synthesis of deuterium labeled compounds are very important for detailed mechanism studies of many chemical reactions,[1] studies on metabolic pathways of biologically important molecules or drug candidates,[2] and retrieving structural details by neutron scattering,[3a] FTIR,[3b] Mass,[3c] and NMR.[3e,f]

There have been reported numerous methods for the introduction of deuterium atom into organic compounds.[4] $LiAlD_4$[2h] or $NaBD_4$-assisted reduction protocol[4k] is the most general method for the preparation of D-incorporated simple organic compounds.

Alkaline hydrolysis of phosphonium salts have been studied extensively,[5] and there is general agreement that the hydrolysis reactions occur by the pathway shown in Scheme 1 as exemplified with benzyltriphenylphosphonium bromide.[5a,b,j,o,q,r] Careful investigation about the stereochemistry and on the kinetics of hydrolysis of phosphonium salts have also been carried out.[5b,j,k,q] Synthesis of D-incorporated compounds by the hydrolysis of phosphonium salts was also studied in part.[5q] However, the classical hydrolysis of phosphonium salt using sodium hydroxide will cause some severe problems for the base-labile substrates. Thus, there will be needed for the mild hydrolysis protocol in order to apply for the base-labile substrates.

Recently, we have reported the synthesis of 5-arylpent-4-enoates via the potassium cyanide-assisted hydrolysis of phosphonium salts, which were derived from the



Scheme 1. General base hydrolysis of phosphonium salts.

Keywords: Deuterium labeled compounds; KCN; Phosphonium salts.
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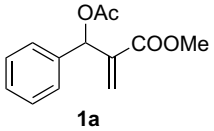
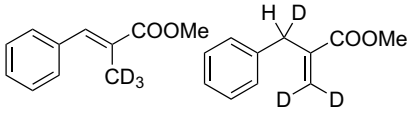
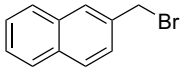
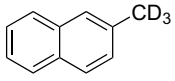
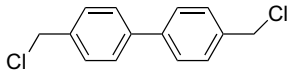
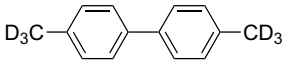
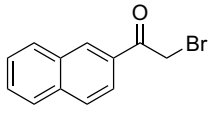
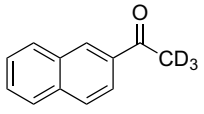
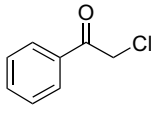
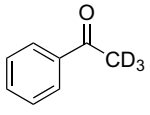
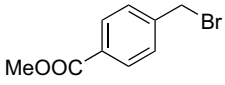
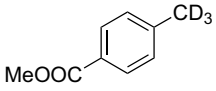
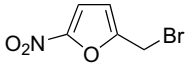
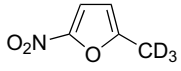
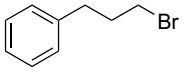
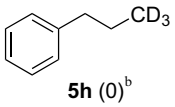
acetates of Baylis–Hillman adducts and phosphorous ylide.[6] During the investigation on the role of cyanide ion for the hydrolysis of phosphonium salts, we envisioned that we could prepare the useful deuterium-labeled compounds easily.

We used the Baylis–Hillman acetate **1a** as the first entry in connection with our recent studies on the chemical transformations of Baylis–Hillman adducts[6,7] and on the reduction of DABCO salts of the Baylis–Hillman acetates with $NaBH_4$.[7h] The reaction of **1a** and triphenylphosphine in H_2O/THF afforded the corresponding phosphonium salt quantitatively. The hydrolysis of the phosphonium salt was examined under various conditions and finally we found that the use of KCN in aqueous THF is the best choice to obtain the desired methyl 2-methylcinnamate.[7h] Without the aid of KCN we could not obtain the hydrolysis product. The use of NaN_3 instead of KCN was ineffective.

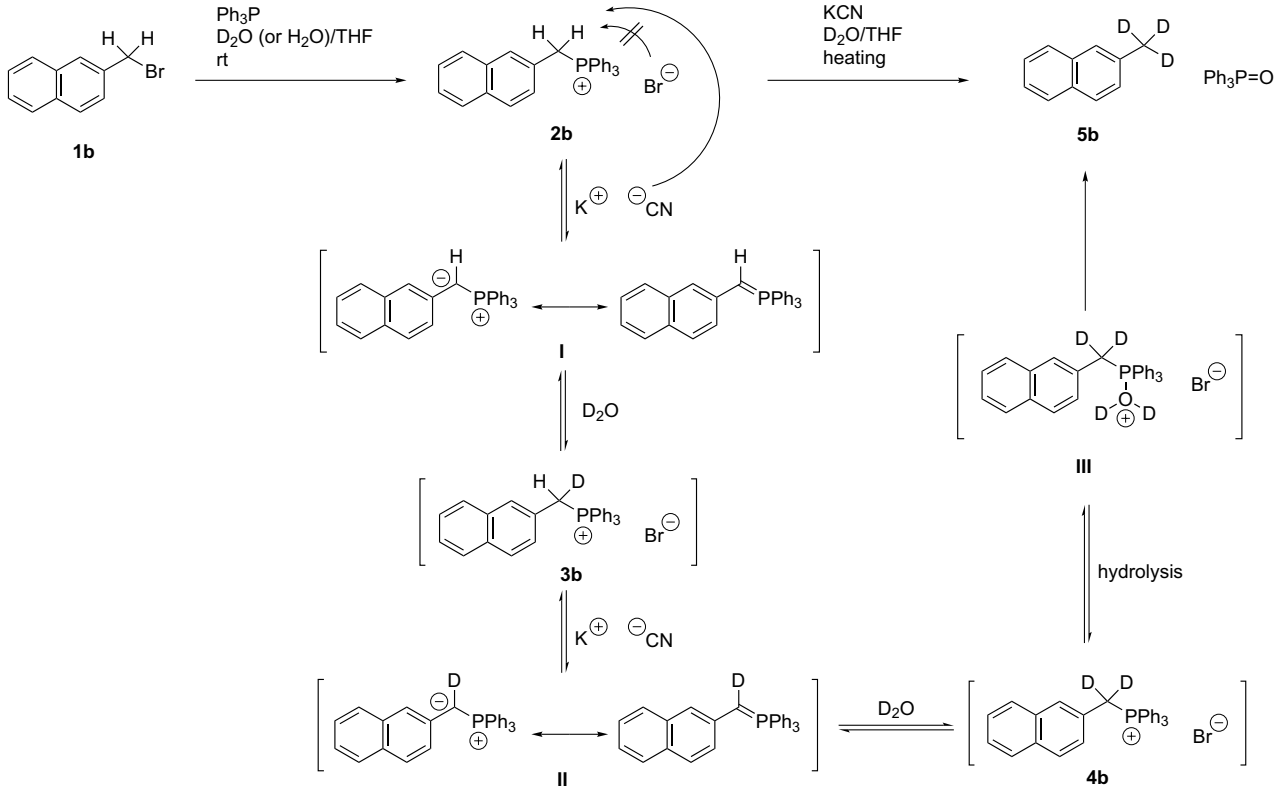
Thus, we carried out the reaction of **1a** in D_2O–THF mixed solvent in order to obtain the corresponding D-labeled compound. As expected we obtained methyl 2-trideuteriomethylcinnamate **5a** as the major product (entry 1 in Table 1). In the ^1H NMR spectrum of **5a**, we found methylene derivative **5a′** was contaminated in about 10%.[8] The mechanism for the formation of **5a** and **5a′** was depicted in Scheme 3 (vide infra).

Table 1. Synthesis of deuterium-labeled compounds **5a–g**

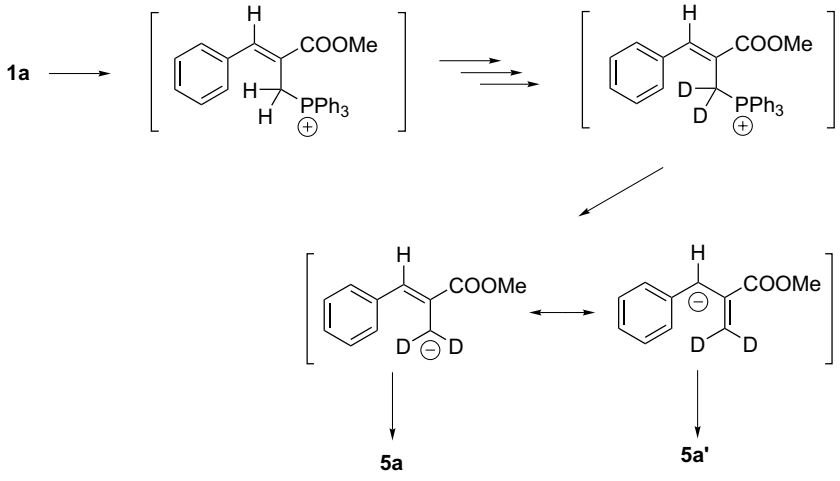
Entry	Substrate	Conditions	Products (% Yield)[a]
1	 **1a**	1. THF/D_2O, Ph_3P (1.2 equiv) rt, 3 h 2. KCN (1.2 equiv) rt, 1 h	 **5a** (81%, 9:1) **5a'**
2	 **1b**	1. THF/H_2O, Ph_3P (1.2 equiv) rt, 12 h, 100% 2. THF/D_2O, KCN (1.1 equiv) 40–50 °C, 13 h	 **5b** (82)
3	 **1c**	1. THF/D_2O, Ph_3P (2.4 equiv) 50–60 °C, 48 h 2. KCN (2.4 equiv) 40–50 °C, 14 h	 **5c** (82)
4	 **1d**	1. THF/D_2O, Ph_3P (1.2 equiv) rt, 20 h 2. KCN (1.2 equiv) 50 °C, 12 h	 **5d** (61)
5	 **1e**	1. THF/D_2O, Ph_3P (1.2 equiv) 50 °C, 36 h 2. KCN (1.2 equiv) 50–60 °C, 48 h	 **5e** (72)
6	 **1f**	1. THF/D_2O, Ph_3P (1.2 equiv) rt, 12 h 2. KCN (1.2 equiv) rt, 24 h	 **5f** (89)
7	 **1g**	1. THF/D_2O, Ph_3P (1.2 equiv) rt, 3 h 2. KCN (1.2 equiv) rt, 3 h	 **5g** (88)
8	 **1h**	1. THF/D_2O, Ph_3P (1.2 equiv) 50–60 °C, 20 h 2. KCN (1.2 equiv) 50–60 °C, 48 h	 **5h** (0)[b]

[a] Mixtures of the corresponding compounds $-CHD_2$, $-CH_2D$, and/or $-CH_3$ were contaminated in trace amounts (2–5%) based on ^1H NMR spectra of **5a–g**.

[b] 4 h was isolated in 80%.[10]



Scheme 2. Proposed reaction mechanism for the conversion of **1b** into **5b**.



Scheme 3.

In order to understand the reaction mechanism we examined the reaction with more structurally simple substrate **1b**. The reaction of **1b** and Ph_3P in D_2O/THF gave the corresponding phosphonium salt **2b** quantitatively.[9] However, the ^1H NMR spectrum of the phosphonium salt at this stage did not show any deuterium incorporation.[9] But, when we performed the following KCN-assisted hydrolysis step in D_2O/THF, we could obtain the deuterium-labeled compound **5b** in 82% yield. From these results we tentatively propose the whole reaction mechanism as in Scheme 2. During the preparation of phosphonium salt the benzylic proton cannot be exchanged with deuterium in solvent. The basicity of bromide ion is so weak that it cannot deprotonate the benzylic proton of **2b**. However, when the KCN was introduced, the cyanide ion can deprotonate the weakly acidic benzylic proton to generate the corresponding ylide **I** in part. Thus, the deuterium–proton exchange can occur to afford **3b** as an intermediate. Same process occurred once again to produce **4b**, and eventually **5b**

according to the well-known hydrolysis mechanism.[5a,b,j,o,q,r] During the last hydrolysis step the cyanide also acts in anyway. But, we cannot say exactly the role of the cyanide ion at this stage.

The representative results are summarized in Table 1. As shown, the reaction can be applicable to both of bromides, chlorides, and acetates. The reaction can be used for the benzylic type and phenacyl type substrates. The reaction can also be applicable to the base-labile substrates like as **1a** or **1f**. However, unfortunately, the hydrolysis of simple alkyl bromides like as 1-bromo-3-phenylpropane (**1h**) failed (entry 8 in Table 1). In this case, as mentioned in earlier papers[5] the corresponding phosphonium salt cannot be hydrolyzed into the desired compound due to the bad leaving group ability of the 3-phenylpropyl anion moiety. Instead, we isolated the corresponding D-labeled phosphonium salt **4h** in 80% yield.[10]

In summary, we developed a facile deuterium labeling method for benzylic halides, allylic acetates, and phenacyl halides. Conversion of the halides or acetates to the corresponding phosphonium salts and the following mild hydrolysis with KCN afforded the deuterium labeled compounds in good yields.

Acknowledgements

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8. Typical procedure for the synthesis of **5b**: A solution of 2-bromonaphthalene (**1b**, 207 mg, 1 mmol) and Ph_3P (315 mg, 1.2 mmol) in D_2O/THF (2 mL, 1:1) was stirred at room temperature for 12 h. To the reaction mixture KCN (72 mg, 1.1 mmol) was added and stirred at 50 °C for 13 h. After usual workup procedure and column chromatographic purification process (hexane/ether, 20:1), **5b** was separated as clear oil, 120 mg (82%). Other D-labeled compounds were prepared similarly and the spectroscopic data are as follows. **5a**: IR (neat) 2214, 2121, 2063, 1712, 1257 cm^{-1}; ^1H NMR ($CDCl_3$) δ (major, **5a**) 3.81 (s, 3H), 7.26–7.39 (m, 5H), 7.70 (s, 1H); (minor, **5a′**) 3.60 (t, $J = 2.1$ Hz, 1H), 3.72 (s, 3H), 7.26–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (major, **5a**) 13.25 (septet, $J = 19.5$ Hz), 51.97, 128.24, 128.30, 128.35, 129.55, 135.80, 138.96, 169.07; (minor, **5a′**) 37.56 (t, $J = 19.5$ Hz), 51.78, 167.30, and other remaining six peaks cannot readable correctly; Mass (70 eV) m/z (rel. intensity) 40 (96), 59 (92), 117 (63), 118 (62), 119 (60), 120 (62), 148 (43), 179 (M^+, 100). **5b**[4n]: IR (neat) 2225, 2202, 2125, 2060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.30 (m, 1H), 7.34–7.44 (m, 2H), 7.58 (s, 1H), 7.69–7.78 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 20.84 (septet, $J = 19.1$ Hz), 124.91, 125.82, 126.82, 127.21, 127.57, 127.65, 128.07, 131.69, 133.65, 135.28; Mass (70 eV) m/z (rel. intensity) 43 (100), 58 (40), 144 (17), 145 (M^+, 28). **5c**[2h]: mp 118–119 °C; IR (neat) 2222, 2129, 2052, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (d, $J = 8.4$ Hz, 4H), 7.46 (d, $J = 8.4$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 20.21 (septet, $J = 19.0$ Hz), 126.77, 129.41, 136.53, 138.28; Mass (70 eV) m/z (rel. intensity) 77 (39), 92 (69), 170 (75), 187 (75), 188 (M^+, 100); **5d**: IR (neat) 2252, 1678, 1284 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52–7.63 (m, 2H), 7.86–8.05 (m, 4H), 8.46 (d, $J = 0.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.19 (septet, $J = 19.5$ Hz), 123.86, 126.76, 127.77, 128.41, 128.46, 129.53, 130.18, 132.49, 134.47, 135.58, 198.23; Mass (70 eV) m/z (rel. intensity) 63 (37), 77 (31), 127 (100), 155 (65), 173 (M^+, 23). **5e**[4o]: IR (neat) 2256, 1682, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.50 (m, 2H), 7.54–7.60 (m, 1H), 7.94–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.17 (septet, $J = 19.1$ Hz), 128.31, 128.58, 133.13, 137.11, 198.33; Mass (70 eV) m/z (rel. intensity) 51 (100), 77 (81), 105 (76), 123 (M^+, 29). **5f**: IR (neat) 2360, 2210, 2129, 2056, 1724, 1281 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.74 (septet, $J = 19.2$ Hz), 51.86, 127.37, 129.00, 129.52, 143.37, 167.12; Mass (70 eV) m/z (rel. intensity) 47 (100), 49 (92), 67 (29), 84 (83), 122 (55), 153 (M^+, 21). **5g**: IR (neat) 2357, 2218, 1493, 1358 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (d, $J = 3.6$ Hz, 1H), 7.25 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.49 (m), 110.04, 113.18, 151.34, 156.80; Mass (70 eV) m/z (rel. intensity) 45 (100), 63 (13), 100 (7), 130 (M^+, 100).
9. In some cases, we separated the phosphonium salt and examined the ^1H NMR spectrum in order to check the D-incorporation. **2b**: ^1H NMR (DMSO-d_6) δ 5.36 (d, $J = 15.9$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 1H), 7.47–7.95 (m, 21H). **2c**: ^1H NMR (DMSO-d_6) δ 5.29 (d, $J = 15.6$ Hz, 4H), 7.04 (d, $J = 8.1$ Hz, 4H), 7.52 (d, $J = 8.1$ Hz, 4H), 7.50–7.92 (m, 30H).
10. ^1H NMR (DMSO-d_6) δ 1.82 (m, 2H), 2.82 (m, 2H), 7.15–7.21 (m, 3H), 7.25–7.31 (m, 2H), 7.74–7.95 (m, 15H).